REMARKS:

Claims 18-21 and 25-104 are withdrawn. Claims 1, 3, and 16 are amended. New claims 105 and 106 are added. Claims 1-17, 22-24, 105, and 106 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

The Examiner noted that color photographs submitted with the application are accepted only for examination purposes unless applicants file a petition under 37 C.F.R. § 1.84(a)(2) and it is granted. The color drawings in Figures 6A and 6B were submitted for examination purposes only and are of sufficient quality that all details in the drawings are reproducible in black and white. Additionally, to assist in an interpretation of a black and white copy of the color photomicrographs in Figures 6A and 6B, the specification provides a brief description of such a black and white reproduction on page 34, lines 2-5.

Claims 15-16 were rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are deposited. The Examiner noted that the deposit of hybridoma producing antibody FM155 would overcome the rejection with respect to claims 15-16 directed to the monoclonal antibody FM155.

Applicants believe that the specification provides adequate disclosure to teach one skilled in the art how to make the FM155 antibody without undue experimentation. However, in an effort to expedite the examination process, applicants assure the Examiner that an acceptable deposit of hybridoma producing the claimed antibody FM155 in compliance with 37 C.F.R. §§ 1.801-1.809 will be made before the date of payment of the issue fee for the instant application. Applicants also assure the Examiner that (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request; (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this

application; (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, which ever is longer; and (d) the deposits will be replaced if they should become nonviable or non-replicable.

Thus, withdrawal of the rejection to claims 15-16 is respectfully requested upon the deposit of the hybridoma producing FM155 antibody. In addition, applicants wish to stipulate that the deposit of the hybridoma does not constitute an admission of inadequate disclosure of FM155 antibody in the specification.

Claims 1-2, 8-14, 17, and 22-24 are rejected under 35 U.S.C. § 102(b) as anticipated by Melvin et al. (WO 97/00449, January 1997 (Melvin)). This rejection is respectfully traversed.

Independent claim 1 has been amended to clarify that the antagonist of the present invention inhibits angiogenesis by modifying protein-protein interactions between a proteolytic enzyme and an integrin. It is an unexpected discovery by the inventors that protein-protein interactions between proteolytic enzymes, such as a matrix metalloproteinase MMP-9, and integrins, such as β1 integrins, contribute to angiogenesis and/or tumor growth by localizing the proteolytic activity to the cell surface (page 5, lines 10-15 and Examples 4-6).

Melvin does not anticipate the present invention. Melvin has no teaching whatsoever of integrins or interactions between proteolytic enzymes and integrins, much less of antagonists that inhibit such interactions. At best, Melvin describes the degradation of basement membrane and interstitial connective tissue of extracellular matrix by MMPs and antibodies inhibiting such degradation (page 1, lines 29-31 and page 4, line 27 – page 5, line 10).

Melvin does not suggest the present invention. Prior to the present invention, it was not known or expected in the art that proteolytic enzymes bind directly with integrins and may co-localize on the surface of a cell and blood vessels. Accordingly, prior to the present invention, those skilled in the art would have not

expected that a modification of an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. Thus, a mere description of MMPs and their well-known substrates, such as basement membrane and interstitial connective tissue of extracellular matrix, without a description of MMP binding to integrins and antagonists inhibiting such binding, would not have made the present invention obvious. Therefore, independent claim 1 is neither anticipated nor rendered obvious by Melvin. Claims 2, 8-14, 17, and 22-24 depend, directly or indirectly, from patentable claim 1 and are, therefore, patentable for at least the same reasons as claim 1.

Claims 1, 3, 6, and 8-13 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ruoslahti et al. (WO 95/14714, 1995, IDS (Ruoslahti)). This rejection is respectfully traversed.

Ruoslahti does not anticipate the present invention. As discussed above, independent claim 1 is directed to an antagonist that inhibits angiogenesis by modifying protein-protein interactions between a proteolytic enzyme and an integrin. Ruoslahti has no teaching whatsoever of proteolytic enzymes or interactions between proteolytic enzymes and integrins, much less of antagonists that inhibit such interactions. At best, Ruoslahti teaches an interaction between integrins and adhesive extracellular matrix proteins (ECM), such as fibronectin, vitronectin, collagens, and laminin (page 1, lines 13-15).

Ruoslahti does not suggest the present invention. As discussed above, prior to the present invention, those skilled in the art would have not expected that a modification of an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. Thus, a mere description of integrins and their well-known substrates, such as ECM proteins, without a description of the direct binding of proteolytic enzymes to integrins and antagonists inhibiting such binding would not have made the present invention obvious. Therefore, independent claim 1 is neither anticipated nor rendered obvious by Ruoslahti.

Claims 3, 6, and 8-13 depend, directly or indirectly, from patentable claim 1 and are, therefore, patentable for at least the same reasons as claim 1.

Claims 1, 3, 6, 8-14, and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by Newton et al., Int'l. Jnl. Oncol., Vol. 6, pages 1063-1070, 1995 (Newton). This rejection is respectfully traversed.

Newton does not anticipate the present invention. Similarly to Ruoslahti, Newton has no teaching of proteolytic enzymes or interactions between proteolytic enzymes and integrins, much less of antagonists that inhibit such interactions. At best, Newton teaches an interaction between $\alpha_5\beta_1$ integrin and fibronectin (abstract).

Newton does not suggest the present invention. As discussed above, prior to the present invention, those skilled in the art would not have expected that a modification of an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. Thus, a mere description of interaction between $\alpha_5\beta_1$ integrin and fibronectin, without a description of direct binding of proteolytic enzymes to $\alpha_5\beta_1$ integrin and antagonists inhibiting such binding, would not have made the present invention obvious. Therefore, independent claim 1 is neither anticipated nor rendered obvious by Newton. Claims 3, 6, 8-14, and 17 depend, directly or indirectly, from patentable claim 1 and are, therefore, patentable for at least the same reasons as claim 1.

Claims 1-14, 17, and 22-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Melvin in combination with Newton. This rejection is respectfully traversed.

As discussed above, Melvin and Newton, when considered separately, do not teach or suggest the instant claim 1. The Examiner acknowledged that Melvin does not teach an antagonist that inhibits an interaction between MMP-9 and at least one amino acid sequence within $\alpha5\beta1$. However, the Examiner appears to believe that "[i]t would have been *prima facie* obvious to combine the antagonist of Melvin ... with the anatagonist of Newton for the purposes of inhibiting tumor metastasis

and angionesis." The Examiner alleges that "one would have been motivated to do so because one would have a reasonable expectation that the combination of the two antagonists to form a new therapeutic antagonist would achieve a greater effect than either antagonist alone based on the successful teachings of Newton..." Applicants respectfully disagree.

First, applicants would like to point out that the antagonists of the present invention are not a simple mixture of two known antagonists, as the Examiner alleges, but novel chemical entities. In this regard, applicants respectfully draw the Examiner's attention to Examples 7-11 of the present specification, which describe antagonists of the present invention. The antagonist of Example 7 is a synthetic peptide, FRIP-9, having the sequence, CysArgLeuArgSerGlyGluProGlnCys or CRLRSGEPQC, representing key amino acids involved in mediating MMP-9/$\alpha 5\beta 1$ interactions. Example 8 shows that FRIP-1 inhibits angiogenesis in chick embryo. The antagonist of Examples 9-11 is the antibody FM155 raised against synthetic peptide FRIP-9.

The antagonists of Newton and Melvin are different from those of the present invention. The antagonists of Newton are monoclonal antibodies specific for $\alpha 5$ or $\beta 1$ integrin subunits, (abstract, page 1064, left column, the paragraph above "Materials and Methods"), not MMP, as in the present invention. The antagonists of Melvin are anti-MMP antibodies specific for MMP-1, MMP-2, or MMP-9 (page 4, lines 10-12). The antibodies were raised against peptides corresponding to amino acid residues 267-277 of MMP-1, amino acid residues 557-569 of MMP-2, and amino acid residues 603-614 of MMP-9 (page 7, lines 12-17). The sequence of MMP-1 peptide is provided in Melvin and is SSFGFRTVKH (page 7, lines 12-13). The sequence of MMP-2 peptide is TSLGLPPDVQRVD and the sequence of MMP-9 peptide is KLGLGADVAQVT according to SwissProt database (see attached reprints of the amino acid sequences for human MMP-2 and MMP-9). Thus, a mechanical mixing of the antagonists of Melvin and Newton suggested by the

Examiner would not have resulted in new chemical entities of the present invention, such as the peptide FRIP-9 and the antibody FM155.

Second, nothing in either Newton or Melvin suggests antagonists that inhibit angiogenesis and/or tumor growth by modifying interactions between proteolytic enzymes and integrins. As discussed above, neither Melvin nor Newton teaches or suggests direct binding between proteolytic enzymes and integrins, much less the effect of such binding on angiogenesis and/or tumor growth. Accordingly, prior to the present invention, those skilled in the art would have not expected that an antagonist inhibiting an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. Thus, applicants respectfully submit that no reason or suggestion for antagonists that modify interactions between proteolytic enzymes and integrins can be found in either reference. Therefore, claims 1-14, 17, and 22-24 are patentable over a combination of Melvin and Newton references.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If the Examiner believes that a telephone conference to discuss this application would be helpful, please call the undersigned attorney at (213) 337-6700.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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